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## **Title**

The boomerang effect – environmental exposure to pharmaceuticals

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## **Keywords**

Pharmaceuticals; environmental exposure modelling; relative risks; risk assessment

## **Abstract**

Nowadays, many pharmaceuticals are detected in surface waters around the world. Because of the extent of the issue, monitoring alone cannot provide a complete overview of the situation. To guide smart monitoring efforts and optimal mitigation measures, spatially explicit models can be used. We show that geographical variability leads to substantial differences in environmental exposure to pharmaceuticals, even at the level of single prescriptions. Application of a multimedia fate modelling approach indicated that in Europe, Spanish infants eating locally produced crops have the highest relative health risks due to exposure to antibiotics. For smaller scale assessments, for example identification of local hotspots or running specific local scenario analyses, we propose the use of geographic-based single-media models.

## **Introduction**

Since ancient times humans have used natural resources for the treatment of disease. Indeed, archaeological evidence suggests that natural antibiotics and laxatives were already used in prehistorical times (Capasso, 1998), and the first structural documentations of Egyptian and Chinese medicine date back more than 3000 years (Raviña, 2011). However, it took until halfway through the nineteenth century for modern day medicine to arise. Facilitated by the emergence of the sciences of pharmacology and synthetic organic chemistry, the already present apothecaries began their transition into pharmaceutical companies (Winqvist et al., 2014). Since then, they have grown into the global enterprises they are today, contributing significantly to the worldwide increase in life expectancy (Roser, 2017). Along the way, the originally empirical chemistry-driven search for new pharmaceuticals shifted towards a target-based biology-driven approach in which new pharmaceuticals are designed rather than discovered. Consequently, newly developed pharmaceuticals have become increasingly effective through designing for potency, bioavailability and

degradation resistance, and many are now globally detected in the aquatic environment (aus der Beek et al., 2016).

Approximately 1500 active pharmaceutical ingredients are currently in use (Guo et al., 2016; Kinch et al., 2014), many of which we are yet unable to detect at environmentally relevant concentrations. Consequently, monitoring will provide at most a patchy and incomplete view of the global situation. There is therefore a need for exposure modelling approaches that can help us prioritize our monitoring efforts and that can be used to take targeted measures. These should preferably be spatially explicit, acknowledging that geographical variability can lead to substantial differences in concentrations across and within regions (Oldenkamp et al., 2016).

## **Methods**

Predicted environmental concentrations (PECs) of chemicals can be derived using multimedia fate models, such as the EUSES model (Vermeire et al., 2005) or our prioritisation tool for APIs (Oldenkamp et al., 2013). Such models are based on mass-balance equations for interconnected compartments that represent the relevant environmental media (e.g., fresh and salt waters, air, urban and agricultural soils, et cetera), and are especially useful for larger scale (regional, continental) assessments where multiple media might be relevant. A typical application is the geographical prioritisation of pharmaceuticals based on their potential human health impact, since human exposure might occur via multiple pathways (e.g., drinking water, crops, fish). Invariably, environmental fate models estimate PECs of pharmaceuticals by integrating information on pharmaceutical usage, human metabolism, removal during wastewater treatment, dilution and dissipation in the receiving environmental compartments, and transport between them. For the estimation of human exposure, environmental concentrations are combined with additional information on the chemical's potential for uptake by crops and fish, and information on consumption and behavioural patterns of the exposed (sub-)population.

## **Results**

Spatially explicit modelling of the environmental medicine chain in Europe identified Spanish infants eating locally produced crops as having the highest relative health risks due to environmental exposure to antibiotics (Figure 1; Oldenkamp et al., 2013). This can be traced back to surplus sewage sludge extensively spread on Spanish agricultural soils. Because of the (semi-)arid climate, antibiotic residues contained in this sludge undergo little runoff to surface waters or leaching into lower soil layers. This makes them available for uptake by crops and subsequent consumption. In fact, the spatial variation in environmental conditions throughout Europe even affects relative impacts at the level of single prescriptions: the environmentally conscious choice between two comparable alternative

pharmaceuticals (e.g. the fluoroquinolones ciprofloxacin and levofloxacin), differs from location to location (Figure 2; Oldenkamp et al., 2014).

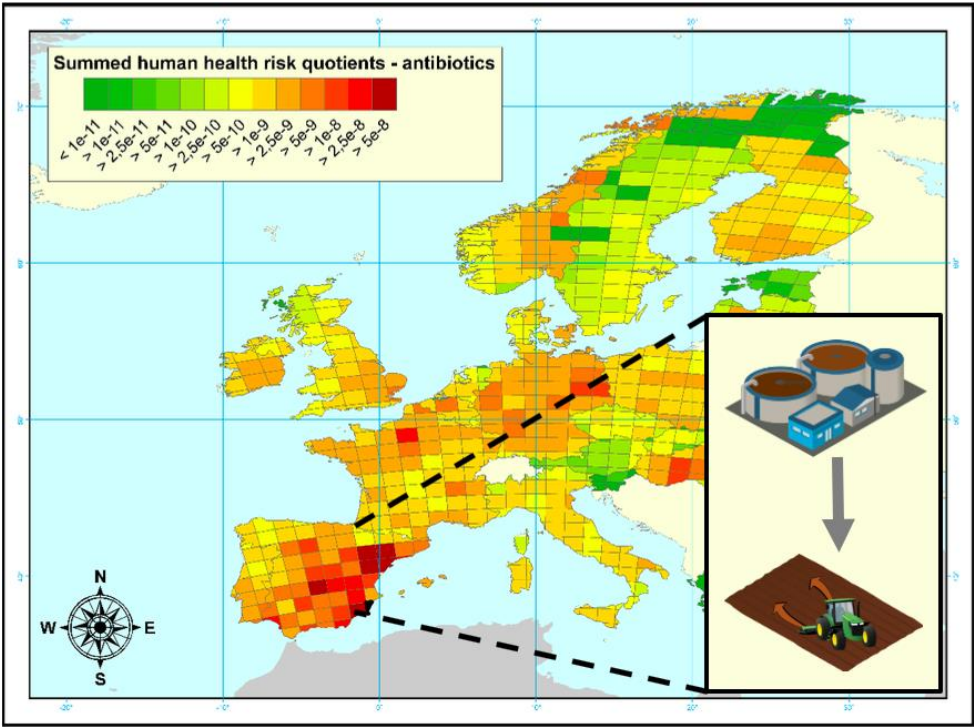


Figure 1. Summed health risk quotients (predicted exposure ÷ HD<sub>50</sub>) for infants in Europe, due to exposure to antibiotics after consumption of locally produced food; inset: visualization of most important exposure route (adapted from Oldenkamp et al., 2013).

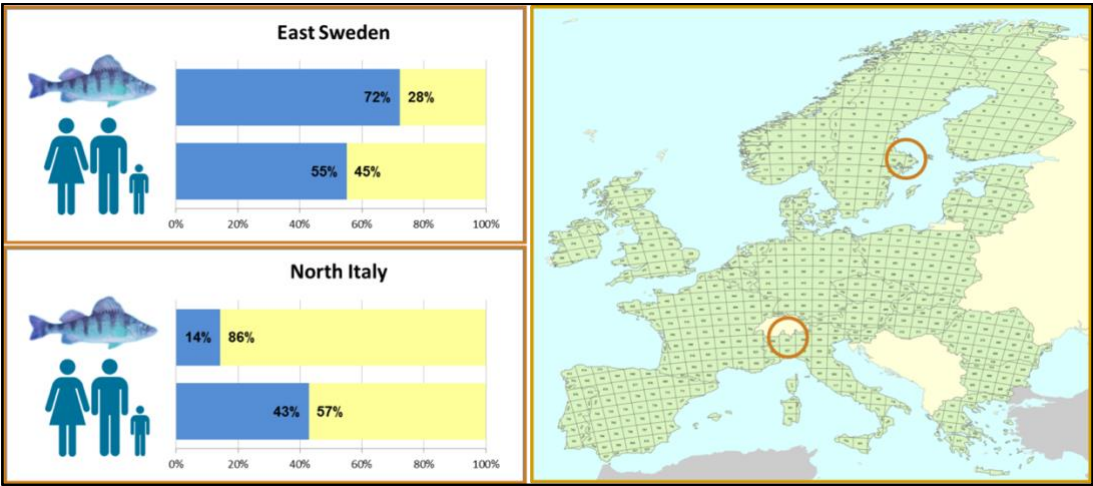


Figure 2. Relative impact of one prescription of ciprofloxacin (blue bars) compared to one prescription of levofloxacin (yellow bars) on the aquatic environment and human health in East Sweden or North Italy (adapted from Oldenkamp et al., 2014).

# Discussion

Relative risks of antibiotics in the environment, based on their potential impacts on human health and the aquatic environment, show substantial geographical variation throughout Europe. Because of their inclusion of multiple environmental media, and the relatively large spatial scale at which they predict, their applicability could be extended in a relative straightforward way to include diffuse sources of veterinary pharmaceuticals. Multimedia fate models are, however, less suitable for answering locally specific questions (e.g., hotspot identification, scenario analyses for optimal mitigation measures), because they assume a homogenous distribution of chemicals over their compartments and do not account for any spatial variation at that scale (Pistocchi et al., 2010). Considering that pharmaceuticals largely remain in the environmental compartment where they are emitted (i.e., surface water or agricultural soils; Żukowska et al., 2006), single-media models form a suitable alternative for local assessments where a single environmental medium is relevant. Examples of geographic-based single-media models for down-the-drain chemicals are GREAT-ER (Feijtel et al., 1997), PhATE (Anderson et al., 2004), GWAVA (Dumont et al., 2012), LF2000-WQX (Williams et al., 2009) and iSTREEM (Kapo et al., 2016).

## Conclusion

Multimedia fate models are suitable tools for the geographical prioritisation of pharmaceuticals in the environment. For the specific case of direct effects of antibiotics, we have shown that a spatially explicit approach to prioritisation is essential.

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